The statutory-type double patenting rejection of Claims 1-4, 6-10, 12-13, 16 and 22 over the specified claims of co-pending Serial No. 08/321,552 is maintained. This rejection is provisional because the conflicting claims in the co-pending case have not been patented. Applicant requests that this rejection be held in abeyance until such time as patentable subject matter is found in either case.

The obviousness-type double patenting rejection of Claims 5, 11, 14-15 and 17-21 over the specified co-pending claims of Serial No. 08/321,552 is also maintained. This is a provisional rejection since the conflicting claims have not, in fact, been patented. Applicant also requests that this rejection be held in abeyance until such time as patentable subject matter is found in either case.

Claims 1-22 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wu *et al.* (WU) in view of Kornguth *et al.* (KORNGUTH). Applicants respectfully traverse.

The references relied upon by the Examiner are summarized as follows. WU teaches the use of complexes with three components: i) a DNA molecule; ii) a polycation; and iii) an asialoglycoprotein molecule which targets the complex to hepatocytes. The complexes of WU function in "delivery of DNA and foreign gene expression in hepatocytes." (page 14338, right column). To effect this function, the compositions of WU specifically bind to hepatocytes and cross the cell membrane thereby delivering the DNA to the hepatocyte where its encoding gene is expressed. The Examiner has acknowledged that WU does not teach or suggest compositions comprising a physiological agent such as a therapeutic or contrast agent.

KORNGUTH describes compositions of polylysine linked to either: i) a metal chelator which binds a metal or ii) a molecule (*e.g.*, Bolton-Hunter reagent) attached to a radioisotope. KORNGUTH emphasizes that these compositions have "a high net positive charge" (*see* Abstract; column 1, line 63; column 2, line 9; column 3, lines 37-43) and, therefore, "will bind selectively to tumors having a higher net negative charge than non-tumor cells." (column 2, lines 9-11). KORNGUTH does not teach or suggest a targeting moiety, since electrostatic interactions are relied upon to provide selective binding to tumors.

The Examiner's position appears to be that since WU can add asialoglycoproteins to polylysine and KORNGUTH can link metals and radioisotopes to polylysine, that there was some motivation to combine the references. Applicants respectfully disagree because the prior art does not suggest the desirability of the combination. M.P.E.P. § 2143.01

As stated in M.P.E.P. § 2142, a *prima facie* case of obviousness requires three basic criteria to be met. First, there must be some suggestion or motivation to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, taken alone or in combination, must teach or suggest all the claim limitations.

In view of these requirements, none of the references, taken alone or in combination, provide any motivation or suggestion to combine the references and practice the claimed invention. WU does not suggest using a metal or radioisotope. KORNGUTH does not teach or suggest using a targeting moiety because KORNGUTH relies on electrostatic interactions to provide selective binding to tumor cells.

Furthermore, the combination of the references renders the prior art unsatisfactory for its intended use and changes its principal of operation. Under these circumstances, the M.P.E.P. § 2143.02 outlines that the desirability of the claimed invention cannot be established. For example, the addition of a nucleic acid which has a high net negative charge to the complex of KORNGUTH would substantially decrease or eliminate the net positive charge of these compositions, thus decreasing or eliminating their selective binding to tumor cells. The attachment of asialoglycoprotein to the composition of KORNGUTH would also decrease binding of KORNGUTH's compositions to tumors because the asialoglycoprotein selectively binds to hepatocytes. The Examiner's statement that the addition of asialoglycoprotein to the compositions of KORNGUTH "*may not* result in a loss of targeting specificity" is irrelevant. The Examiner has acknowledged that KORNGUTH's compositions require a high net positive charge to bind tumor cells, that DNA is negatively charged, and that asialoglycoprotein is a hepatocyte targeting moiety. Therefore, the addition of DNA and/or asialoglycoprotein to the compositions of KORNGUTH changes their principal of operation and renders these compositions unsatisfactory for binding to tumors via electrostatic interactions.

In rebuttal to Applicants' previous response, the Examiner has cited several passages in the specification relating to the utility of electrically neutral compositions and concludes:

> Hence, based on the disclosure of Applicant's specification, it is unclear how Kornguth *et al.* teaches away from the instant invention by the addition of a nucleic acid to polylysine because such statement 'appears' to contradict what is claimed and disclosed in Applicant's specification.

Applicants have no comment in regards to the Examiner's interpretation of the cited passages; however, the Examiner is respectfully reminded that the motivation to practice the claimed invention must be found in the prior art rather than Applicant's disclosure. The M.P.E.P. § 2143 outlines:

> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

By citing the specification, the Examiner is using hindsight analysis which the M.P.E.P. § 2145 X.A. states is an improper rationale for combining references:

> [a]ny judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure". *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209,212 (CCPA 1971).

In *In re Fitch* the Federal Circuit noted:

> [I]t is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious.... This court has previously stated that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." (972 F.2d at 1266, 23 USPQ2d at 1784)

Therefore, Applicants respectfully assert that the Examiner's arguments are improper.

In response to the Examiner's position that KORNGUTH "is relied upon for its teachings of coupling polylysine to a linking group and imaging agent or chemotherapeutic agent", Applicants respectfully point out that a reference must be viewed in its entirety.

> A prior art reference must be considered in its entirety, i.e., as a whole, including portions what would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). M.P.E.P. § 2141.02

In *In re Wesslau (1965)*, the Court of Customs and Patent Appeals held:

> it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. (353 F.2d at 241, 147 USPQ at 393)

Therefore, it is incumbent upon the Examiner to view the cited references in their entirety rather than for disclosing only that which the Examiner believes supports his position.

In conclusion, neither reference, taken alone or in combination, provides the required motivation to combine the references. As acknowledged by the Examiner in the Office Action dated October 24, 1996, page 4, WU does not disclose the inclusion of an MRI agent. As argued above and in the response of March 11, 1999, KORNGUTH does not provide the required motivation to combine the references, as i) the combination would render the KORNGUTH system unsatisfactory for its intended purpose, ii) the combination would alter the mechanism by which the KORNGUTH system functions, and iii) it actually teaches away from the combination in that a loss of targeting could occur.

Finally, the Applicants respectfully remind the Examiner that the Supreme Court of the United States has stated that "such secondary considerations as commercial success, long felt but unsolved needs, failure of others, *etc.*, might be utilized to give light to the circumstances surrounding the origins of the subject matter sought to be patented." *Graham v. John Deere Co.*, 148 USPQ 459 (1966). Therefore, Applicants respectfully request the Examiner to reconsider the objective evidence provided in the response of March 11, 1999.

Based on the foregoing, Applicants respectfully submit that the rejection under section 103 is improper and respectfully request that it be withdrawn.

CONCLUSION

Applicants respectfully submit that the now pending claims are in condition for allowance. An early notification to that effect is respectfully requested. If a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON HERBERT LLP

Richard F. Trecartin, Reg. No. 31,801

Four Embarcadero Center, Suite 3400
San Francisco, California 94111-4187
Telephone: (415) 781-1989

622132.DSS

APPENDIX:

1. A delivery vehicle comprising:
   a) a first polymeric molecule having a net positive or negative charge,
   b) at least one second polymeric molecule having a net charge opposite that of said first polymeric molecule and complexed with said first polymeric molecule, said second polymeric molecule having attached thereto at least one cell targeting moiety, and
   c) at least one physiological agent attached to said first or second polymeric molecule or to a third polymeric molecule, wherein said third polymeric molecule, if present, has a net charge opposite that of said first polymeric molecule and is complexed with said first polymeric molecule.

2. A delivery vehicle according to claim 1 wherein said first polymeric molecule comprises a nucleic acid.

3. A delivery vehicle according to claim 2 wherein said nucleic acid is DNA.

4. A delivery vehicle according to claim 3 wherein said DNA encodes a polypeptide.

5. A delivery vehicle according to claim 3 wherein said polypeptide is herpes thymidine kinase protein.

6. A delivery vehicle according to claim 2 wherein said second polymeric molecule comprises a polyamine.

7. A delivery vehicle according to claim 6 wherein said third polymeric molecule is present and comprises a polyamine.

8. A delivery vehicle according to claim 6 wherein said second polymeric molecule is selected from the group consisting of polylysine and spermidine.

9. A delivery vehicle according to claim 7 wherein said second polymeric molecule comprises polylysine or spermidine and said third polymeric molecule comprises polylysine or spermidine.

10. A delivery vehicle according to claim 1 wherein said physiological agent comprises a contrast agent.

11. A delivery vehicle according to claim 10 wherein said contrast agent comprises a paramagnetic ion complexed with a chelator.

12. A delivery vehicle according to claim 11 wherein said paramagnetic ion is gadolinium.

13. A delivery vehicle according to claim 12 wherein said chelator comprises diethylenetriaminepentaacetic acid (DTPA) or 1,4,7,10-tetraazacyclo-dodecane-N,N′,N″,N‴ tetracetic acid (DOTA).

14. A delivery vehicle according to claim 1 wherein said physiological agent is a therapeutic agent.

15. A delivery vehicle according to claim 14 wherein said therapeutic agent is a selected from the group consisting of phototherapeutic agents and anti-cancer agents.

16. A method of delivering a nucleic acid to a cell comprising:
(a) contacting said cell with a nucleic acid delivery vehicle comprising:
    i) a nucleic acid,
    ii) at least one first polycationic molecule complexed with said nucleic acid, said first polycationic molecule having attached thereto at least one cell targeting moiety for a surface receptor on said cell, and
    iii) at least one contrast agent attached to said first polycationic molecule or to a second polycationic molecule, wherein said second polycationic molecule, if present, is complexed with said nucleic acid, and
(b) detecting the presence of said contrast agent in said cell as an indication of whether said nucleic acid has been delivered to said cell.

17. A method of delivering physiological agents to a cell comprising:
a) contacting said cell with a delivery vehicle comprising:
    i) a first polymeric molecule having a net positive or negative charge,
    ii) at least one second polymeric molecule having a net charge opposite that of said first polymeric molecule and complexed with said first polymeric molecule, said second polymeric molecule having attached thereto at least one cell targeting moiety for a surface receptor on said cell, and
    iii) at least one physiological agent attached to said first or second polymeric molecule or to a third polymeric molecule, wherein said third polymeric molecule, if present, has a net charge opposite that of said first polymeric molecule and is complexed with said first polymeric molecule; and
b) detecting the presence of said physiological agent in said cell as an indication of whether said physiological agent has been delivered to said cell.

18. A method according to claim 17 wherein said physiological agent is a contrast agent.

19. A method according to claim 17 wherein said physiological agent is a therapeutic agent.

20. A method according to claim 17 wherein said delivery vehicles comprise at least one contrast agent and at least one therapeutic agent.

21. A method according to claim 18 or 20 wherein said detection is by magnetic resonance imaging (MRI).

22. A delivery vehicle comprising:
a) a first polymeric molecule having a net positive charge and having hydrophobic residues that facilitate cellular uptake of said delivery vehicle,
b) a second polymeric molecule having a net negative charge and complexed with said first polymeric molecule, and
c) at least one physiological agent attached to said first or second polymeric molecule.